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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/993,363	11/14/2001	Philip G. Ashton-Rickardt	ARCD:382US	5741

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EXAMINER	
SHUKLA, RAM R	
ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 03/19/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/993,363	Applicant(s) ASHTON-RICKARDT ET AL.	
	Examiner Ram R. Shukla	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 January 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-60* is/are pending in the application.

4a) Of the above claim(s) *1-25 and 51-60* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26-50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 10.6 RRS
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. The Examiner prosecuting this application has been changed. Any inquiries relating to the examination of the application should be directed to Examiner Shukla, whereas any inquiries relating to formal matters should be directed to Ms. Tabb, Patent Analyst. The phone numbers for Examiner Shukla and Patent Analyst Tabb are provided at the end of this office action.

2. Applicant's election without traverse of the invention of group II, claims 26-50 in Paper No. 9 of 1-14-03 is acknowledged. It is noted that the HIV and PI9 have been elected as species for prosecution and the specification does not teach how to induce immunity in a HIV infected subject or any subject with any disease by the claimed method.

3. Claims 1-25 and 51-60 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 9.

4. Claims 26-50 are under consideration.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 26-50 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claimed invention encompasses a method that comprises an expression vector that encodes a granzyme inhibitor. However, the specification does not provide sufficient written description support for the claimed genus of granzyme inhibitors. Dependent claims also recite granzyme inhibitors that inhibit activity, transcription, translation, and degradation of granzyme or destabilize granzyme. In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. When the claims are analyzed in light of the specification, instant invention recites a genus, a granzyme inhibitor. However, the specification does not teach what is the complete structure of representative number of species of the genus. Additionally, claims also recite inhibitors of activity, transcription, translation, degradation of granzyme or that destabilize granzyme. However, the specification does not teach what would be the structure of a species of each subgenus.

Next, then, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (i.e. other than nucleotide sequence), specific features and functional attributes that would distinguish different members of the claimed genus. In the instant case, the only other identifying characteristic is that the inhibitor inhibits transcription, translation, and degradation of granzyme or destabilize granzyme. The specification does not disclose any identifying characteristic as to how an artisan would have differentiated different inhibitors. Again, the members of any of these subgenuses themselves may have very different structure and the specification does not provide any description of any identifying characteristics of the species of the subgenuses.

Accordingly, this limited information is not deemed sufficient to reasonably convey to one skilled in the art that the applicant is in possession of the broad genus of the modulators or agents at the time the application was filed. Thus it is concluded that the specification does not meet the written description requirements.

7. Claims 26-50 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a

way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claimed invention is drawn to a method of inducing immunity or enhancing immunity in any subject with any disease, such as cancer, viral infection with any granzyme inhibitor wherein the subject is either administered an expression vector or cytotoxic T-lymphocytes comprising the expression. However, the specification as filed does not provide sufficient guidance for an artisan of skill to make and use the claimed invention and an artisan of skill would have required undue experimentation to practice the claimed invention because the art of gene therapy or therapy of a disease with CTLs is unpredictable and the specification does not provide any guidance as to how to address the issues of unpredictability in the art. It is noted that the HIV and PI9 have been elected as species for prosecution and the specification does not teach how to induce immunity in a HIV infected subject or any subject with any disease by the claimed method.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The specification as filed teaches general teachings of making vectors, expression system, viral vectors etc. The specification also reviews the role of serpins in apoptosis regulation. The specification also teaches vector for expressing SPI6 and PI-9. The specification teaches working example of in vitro effect of SPI6 on viability and function of CTLS (see the working examples). The specification also teaches a transgenic mouse over expressing SPIS wherein the human CD2 promoter directs the expression of SPI6 in NK cells, mature T cells and thymocytes (see example 3). However, the specification does not teach any effect of either SPI6 or PI-9 or any other granzyme inhibitor on immunity in vivo in any disease model. It is noted that the SPI6 mouse is not an art recognized model for any disease or for HIV.

The claimed invention is not enabled by the instant specification because the art of gene therapy and of cell therapy using CTLs is unpredictable as recognized in the art. Clay et al (Clark TM et al. Pathology Oncology Research 5:3-15, 1999) look at the some of the technical and biological hurdles that need to be addressed in gene therapy trials and conclude, "Unfortunately, no gene therapy trial to date has been conclusively proven to be effective in treating the targeted disease.....It is clear that greater emphasis should be placed in vector development and understanding the biology of gene therapy targets if we expect gene therapy to be a viable option in the future..... Further advances will also be required in vector development and in establishing the optimum transduction conditions for target cells to enhance the efficiency of gene transfer and to provide prolonged gene expression."

Romano et al (Romano et al. Stem Cells 2000; 18:19-39) reporting on the recent developments of gene therapy, noted," However, the real effectiveness of gene therapy programs is still in question. After a decade of clinical trials, the therapeutic applications of gene transfer technology are still at a rather preliminary stage."

It is noted that these reviews by the leaders in the field of gene therapy are about those gene therapy protocols and applications where the mechanism of action and some efficacy has been determined in animal models and there may be

some extrapolatable correlations indicating the therapeutic effects of a particular gene's encoded protein. Even with such results, it is uncertain whether there would be a therapeutic effect when the studies obtained in a mouse model or another animals model is extended to a human subject.

In particular, in case of claims 26-29, claims encompass administration of the expression vector by any route and then the vector has to reach CTLs and expressed in there. However, the specification does not teach as to how the DNA administered by any route will be directed to CTLs such that sufficient amount of inhibitor peptide is produced. While the claims reciting using a promoter specific to CTLs, there is no evidence and direction as to how the expression vector will reach the CTLs in the first place and in sufficient amounts. It is noted that the specification has used a SPI6 expressing transgenic mouse, which was infected with LCMV. However, this is not a natural animal model because there is no issue of gene delivery to cells since the mouse has the transgene in all of its cells, however, a subject can not be made transgenic for a transgene such as SPI6 and therefore, one can not predict whether the gene of interest can reach the target cells in sufficient amounts. The specification does not provide any guidance regarding this. Additionally, the claimed invention encompasses any inhibitor, again the specification does not teach as to how any inhibitor will be expressed and the method practiced.

Next, claims 30-50 encompass CTLs derived from any source and administered to any subject which will included CTLs of autologous, allogeneic or xenogeneic origin or from any subject with any disease or condition and administered to any subject with any disease or condition. It is debated in the art whether CTLs can be effectively used in treating HIV. For example, Bordie et al Nature Medicine 5:34-41, 1999), while reviewing the state of the art of HIV-1 specific CTLs noted that while primary infection is associated with a vigorous CTL response, HIV-specific CTLs seem to be primarily localized to blood rather than lymph nodes (see second paragraph in the left column on page 34). Another limitation of the method they argue is that the in vivo activity of the transferred CTLS can not be assessed as persistence was limited by the induction of a host CTL

response to foreign proteins, such as to HSV Tk or hygromycine phosphotransferase used for selecting cells in culture. It is emphasized that the specification does not teach how to specifically teach inducing or enhancing immunity in a subject against HIV. In fact there are only two references to HIV in the specification, one on page 2, lines 17-24 and page 8, lines 13 and none of these sections provide any specific teaching as to how an artisan have practiced in a subject with HIV infection. Tan et al (Blood 93:1506-1510, 1999) in their study on the death of adoptively transferred T cells in AIDS, noted, "Because trials of adoptive cell transfer in HIV are laborious and infrequent, the generality of these findings will need to be confirmed by different groups. Subsequent trials should take into account the vulnerability of cells culture in vitro to apoptosis and use means for quantifying their survival in vivo. Engineering apoptosis-resistant antigen specific CTL may circumvent the obstacle, but the success of this strategy depends on better elucidating the mechanism of cell death in vivo". The specification does not address the issue of cell culture and how the cells will be quantified in vivo and what will be the fate of the cells in vivo. In yet another review article, McMichael et al reviewed the state of the art of the complexity of cellular response to HIV and noted that it was not clear what functions of CTLs are most important for controlling HIV and that knockout mice for Perforin while do not recover from LCMV infection, these mice handle other viral infections effectively which indicates that the granzyme and perforin mediated cell lysis may not be mechanistically same in all the viral infections (see page 981, right column). In other words, one would not expect to see same type of effect of granzyme inhibitor on immunity for any virus. Therefore, one will question whether the results disclosed in the specification are applicable to HIV or any other virus.

It is noted that claims 31-33 recite different viral vectors, however, the specification except for providing general description of vectors, does not provide any specific details. It is noted that it is recognized in the art that vectors are one of the major limitations of a method of gene therapy. As noted by Clay et al, "It is clear that greater emphasis should be placed in vector development and understanding the biology of gene therapy targets if we expect gene therapy to be a viable option in the future..... Further advances will also be required in

vector development and in establishing the optimum transduction conditions for target cells to enhance the efficiency of gene transfer and to provide prolonged gene expression."

Claim 34 recites inhibitors that inhibit anything from granzyme activity to transcription, translation etc., however, the specification does not teach how to make all these inhibitors and administer them to a subject either as expression vector or as a cell comprising the expression vector so as to effect enhancement or induction of immunity. Regarding claims 48-50, it is noted that in view of the unpredictability issues discussed above, an artisan would not have been able to increase number of CTLs or augment CTL function or augment memory cell development.

In conclusion, the art of gene therapy and CTL therapy is highly unpredictable in general. Thus, the cited prior and post-filing art clearly indicates an unpredictable status of the gene therapy art. And, although, specific vectors, promoters, genes, and routes of administration might be or may have been effective for treatment of a specific disease providing a specific therapeutic effect, gene therapy as a broad-based art is clearly unpredictable in terms of achieving levels and duration of expression of a gene of interest which results in a therapeutic effect. The courts have stated that reasonable correlation must exist between scope of a right to exclude a patent application and scope of enablement set forth in patent application. 27USPQ2d 1662 *Ex parte Maizel*. Scope of Enablement is considered in view of the Wands factors (MPEP 2164.01 (a)). Accordingly, in view of the quantity of experimentation necessary to determine the parameters for achieving treatment of any and all disease/disorder and any and all routes of administration as broadly claimed, the lack of direction or guidance provided by the specification was well as the absence of working examples with regard to a therapeutic effect, it would have required undue experimentation of one skilled in the art to use the claimed invention as broadly claimed.

8. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ram R. Shukla whose telephone number is (703) 305-1677. The examiner can normally be reached on Monday through Friday from 7:30 am to 4:00 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051. The fax phone number for this Group is (703) 308-4242. Any inquiry of a general nature, formal matters or relating to the status of this application or proceeding should be directed to the William Phillips whose telephone number is (703) 305-3413.

Ram R. Shukla, Ph.D.
Primary Examiner
Art Unit 1632

Ram R. Shukla
RAM R. SHUKLA, PH.D
PATENT EXAMINER